AMENDMENTS TO THE SPECIFICATION

Please amend the specification as follows. Consideration and entry of these amendments are respectfully requested.

Please amend the paragraph bridging pages 1-2 (page 1, line 30 through page 2, line 6) as follows:

The specific cytokines produce by polarized Th cells are the primary effectors that promote differentiation of precursor Th (Thp) cells, but these cells also cross-regulate the other subset's functional activity. For example IL-4 is reported to be a potent factor in promoting the differentiation of Thp cells to Th2 effectors. In addition, IL-4 antagonizes production of IFNγ. IL-10, another cytokine produced by Th2 cells, has also been described to inhibit Th1 development and IFNγ-induced macrophage function. Conversely, the IFNγ produced by Th1 cells amplifies Th1 development and inhibits the expansion of Th2 cells. The ability of these cytokines to promote ~~to promote~~ development of specific Th cell subsets, while simultaneously inhibiting the alternate developmental fate, results in progressively polarized response.

Please amend the first full paragraph of page 3 (lines 7-14) as follows:

In another aspect, the invention features a method for promoting differentiation of a Th precursor (Thp) cell or cell population into a Th2 cell or cell population. In one embodiment, the method includes contacting the Thp cell or cell population with an IL-21 agonist in amount sufficient to induce differentiation of the Thp cell or cell population into a Th2 cell or cell population, and the agonist is an IL-21

polypeptide having an amino acid sequence that is at least 85% identical to SEQ ID NO: 2 and which is capable of binding to an IL-21R. In some embodiments, the ~~methodfurther~~ method further includes identifying a Thp cell or cell population in which differentiation into a Th2 cell or cell population is desired.

Please amend the final paragraph of page 3 (lines 25-28) as follows:

[[In]] In some embodiments of these methods, the polypeptide ~~includesthe~~ includes the amino acid sequence of SEQ ID NO:2. In some embodiments of these methods, the contacting step is carried out ex vivo, in vitro, or in vivo. A suitable subject for ex vivo or in vivo methods includes a mammalian subject, for example, a human.

Please amend the first paragraph of page 4 (lines 1-10) as follows:

In another aspect, the invention features a method for inhibiting differentiation of a Th precursor (Thp) cell or cell population into a Th2 cell or cell population. The method includes contacting the Thp cell or population with an antagonist of an interleukin-21 (IL-21)/IL-21 receptor (IL-21R) in an amount sufficient to inhibit differentiation of the Thp cell or cell population into the Th2 cell population, and the antagonist is selected from the group consisting of an ~~anti-IL21R~~ anti-IL-21R antibody, an antigen-binding fragment of an ~~anti-IL21R~~ anti-IL-21R antibody and a soluble fragment of an IL-21R. The method optionally further includes identifying a T cell or cell population in which ~~an~~ inhibition of differentiation of a Thp cell or cell population into a Th2 cell or cell population is desired. In some ~~embodiment~~ embodiments, the T cell population includes at least one Th1 cell.

Please amend the second paragraph of page 4 (lines 12-18) as follows:

In some ~~embodiments,he~~ embodiments, the soluble fragment of an IL-21R includes an extracellular region of an IL-21 Receptor. For example, the soluble fragment can include an amino acid sequence at least 85% identical to amino acids 20 to 235 of SEQ ID NO: 4 and which is capable of binding IL-21; alternatively, the soluble fragment includes amino acids 1 to 235 of SEQ ID NO:4. In related embodiments, the soluble fragment further includes an Fc fragment. In yet another embodiment, the antagonist is an ~~anti-IL21R~~ anti-IL-21R antibody or an antigen-binding fragment of the ~~anti-IL21R~~ anti-IL-21R antibody.

Please amend the third paragraph of page 4 (lines 19-21) as follows:

In yet ~~anotherembodiment~~ another embodiment, the contacting step is carried out ex vivo, in vitro or in vivo. The contacting step can be carried out in a mammalian subject, for example, the mammalian subject is a human.

Please amend the last paragraph of page 4 (lines 23-29) as follows:

In another aspect, the invention features a method for increasing interferon gamma (IFNγ) levels in a T cell or cell population. The method in one embodiment includes contacting the T cell or cell population with an antagonist of an IL-21/IL-21R in an amount sufficient to increase IFNγ levels in the T cell or cell population, and the antagonist is selected from the group consisting of an ~~anti-IL21R~~ anti-IL-21R antibody, an antigen-binding fragment of an ~~anti-IL21R~~ anti-IL-21R antibody and a soluble fragment of

an IL-21R. An embodiment of this method further includes identifying a T cell population in which an increase in IFNγ levels is desired.

Please amend the first paragraph of page 5 (lines 1-7) as follows:

In some embodiments,[[,]] the soluble fragment of an IL-21R includes an extracellular region of an IL-21 Receptor. For example, in some embodiments the soluble fragment comprises an amino acid sequence at least 85% identical to amino acids 20 to 235 of SEQ ID NO:4 and which is capable of binding IL-21; alternatively, the soluble fragment includes amino acids 1 to 235 of SEQ ID NO:4. In related embodiments, the soluble fragment further includes an Fc fragment. In yet another embodiment, the antagonist can be an ~~anti-IL21R~~ anti-IL-21R antibody or an antigen-binding fragment of the ~~anti-IL21R~~ anti-IL-21R antibody.

Please amend the fifth paragraph of page 6 (lines 9-10) as follows:

FIG. 3A is a graphic representation of IL-4 and IFNγ production in Thp cells cultured under Th1 skewing conditions in the presence or absence of ~~IL-22~~ IL-21.

Please amend the ninth paragraph of page 6 (lines 17-18) as follows:

FIG. 4B is a histogram showing ~~relative~~ levels of IL-12Rß2 mRNA relative to levels in Th1 cells.

Please amend the last paragraph of page 6 (lines 25-26) as follows:

FIG. 5A is a graph showing specific swelling in TNP-KLH-immunized wild type and ~~IL21-21R-/- mice~~ IL-21R-/- mice subsequently injected with TNP-KLH or PBS.

Please amend the first paragraph of page 7 (lines 1-2) as follows:

~~FIG.5B~~ FIG. 5B is a histogram showing IFNγ production in CD4+ T cells purified from draining lymph nodes of TNP-KLH-immunized wild type and ~~IL21-21R-/- mice~~ IL-21R-/- mice restimulated by antigen.

Please amend the first full paragraph of page 8 (lines 3-12) as follows:

In one embodiment, a method for reducing or inhibiting the activity or level of IFNγ in a cell, e.g., a T cell (e.g., a T cell precursor cell (a Thp cell), or a Th1 cell (e.g., a differentiating Th1 cell or an effector Th cell)), or a cell population thereof is provided. The method includes (optionally) identifying a cell, e.g., a T cell, or a cell population, e.g., a T cell population, in which reduction or inhibition of the activity or level of IFNγ is desired; and contacting said cell or cell population with an amount of an IL-21 agonist, sufficient to reduce or inhibit the activity or level of IFNγ in said cell or cell population. Preferably, the ~~Il-21~~ IL-21 agonist specifically inhibits IFNγ levels or activity, e.g., it does not reduce or inhibit the activity or level of other cytokines such IL-2 or TNFα. In one embodiment, the IL-21 agonist inhibits production of IFNγ by an IFNγ-producing cell, e.g., an IFNγ-producing Th1 cell.

Please amend the first full paragraph of page 13 (lines 1-10) as follows:

Alternatively, the method can be performed on cells (e.g., immune or T cells as described herein) present in a subject, e.g., as part of an in vivo (e.g., therapeutic or prophylactic) protocol. For example, the method can be used to treat or prevent a Th1-mediated disorder, e.g., an autoimmune disorder (e.g., multiple sclerosis, rheumatoid arthritis, type I diabetes, Crohn's disease, psoriasis and myasthenia gravis, among others), in a subject. Accordingly, the invention provides a method of treating (e.g., curing, suppressing, ameliorating, delaying or preventing the onset of, or preventing recurrence or relapse of) or preventing a Th1-associated disorder in a subject. The method ~~include~~ includes administering to a subject an IL-21 agonist in an amount sufficient to inhibit or reduce Th1 cell activity and/or cell number, thereby treating or preventing a Th1-associated disorder.

Please amend the last paragraph of page 39 (lines 20-29) as follows:

To determine whether the potential to express IL-21 increases as cells develop along a Th2 pathway, IL-21 expression in primary stimulated Thp cells was compared to ~~Il-21~~ IL-21 message expression in secondary stimulated Th2 cells. The results are shown in FIG. 1B. For the results shown, Thp cells were cultured under neutral, Th1 and Th2 skewing conditions. RNA was purified 24 hours after primary and secondary anti-CD3 stimulation. Cytokine expression was assessed in duplicate by RealTime PCR and shown relative to GAPDH. IL-21 message, like IL-4, was observed to be relatively low in Thp cells after primary stimulation. In contrast, ~~Il-21~~ IL-21 expression was markedly increased after cells were allowed to differentiate along the Th2 pathway. These results

demonstrate that ~~Il-21~~ IL-21 gene expression is regulated similarly to other Th2-specific cytokines.